REMARKS

Entry of the Amendment and reconsideration of the claims in view of the following Remarks is respectfully requested.

Claim 39 is cancelled without prejudice or disclaimer. Applicants reserve the right to pursue the subject matter of this claim in one or more continuation applications.

Claims 30, 37, 43, 50, and 51 have been amended. No new matter is added by the amendments.

Withdrawn Rejections/Objections

The Applicants acknowledge the withdrawal of the objection of claim 52 for being of improper dependent format.

The Applicants acknowledge the withdrawal of the rejection of claims 50 and 53-55 under 35 U.S.C. 112, first paragraph, for lack of written description.

Double Patenting

Applicants acknowledge the provisional rejection of claims 30-43, 45-51 and 53-55 under the judicially created doctrine of obviousness-type double patenting as unpatentable over claims 88-109 of co-pending Application No. 09/863,693. Applicants request that the Examiner hold this rejection in abeyance until notice of allowable subject matter.

Applicants acknowledge the provisional rejection of claims 30-43, 45-51 and 53-55 under the judicially created doctrine of obviousness-type double patenting as unpatentable over claims 47-63 of co-pending Application No. 09/520,130. Applicants request that the Examiner hold this rejection in abeyance until notice of allowable subject matter.

Applicants acknowledge the provisional rejection of claims 30-43, 45-51 and 53-55 under the judicially created doctrine of obviousness-type double patenting as unpatentable over claims 45-82 of co-pending Application No. 10/143,437. Applicants

request that the Examiner hold this rejection in abeyance until notice of allowable subject matter.

35 U.S.C. 112, second paragraph

Claim 51 was rejected under 35 U.S.C. 112, second paragraph, as indefinite. The Applicants traverse this rejection. While not acquiescing to the rejection and solely to expedite prosecution, Applicants' claim 51 no longer refers to "each".

Claims 30-43, 45-49, 50, 51 and 53-55 were rejected under 35 U.S.C. 112, second paragraph, as indefinite. The Applicants traverse this rejection.

Claim 30 was rejected as indefinite for lack of antecedent basis and for lack of clarity. While not acquiescing to the rejection and solely to expedite prosecution, Applicants have amended claim 30 as suggested by the Examiner.

The Examiner contends claim 37 is indefinite because of a phrase in the claim. While not acquiescing to the rejection and solely to expedite prosecution, claim 37 has been amended as suggested by the Examiner.

The Examiner contends claim 43 is indefinite because of the first instance of "interface". While not acquiescing to the rejection and solely to expedite prosecution, Applicants have amended the claim as suggested by the Examiner.

Applicants respectfully request withdrawal of the 35 U.S.C. § 112, second paragraph, rejection of the claims.

35 U.S.C. 112, first paragraph

Claims 30-42 were rejected under 35 U.S.C. 112, first paragraph, for allegedly containing new matter. Although the Applicants do not concede the propriety of this rejection, the claims have been amended to address the Examiner's concerns. The Applicants submit that claims 30-42 are fully supported by the specification as filed, and withdrawal of the rejection is therefore respectfully requested.

35 U.S.C. § 1.75(c)

The Examiner rejected claim 39 as being of improper dependent form. Applicants have cancelled this claim rendering the rejection moot. Applicants request withdrawal of the objection.

35 U.S.C. 102(b)

Claims 30, 40, 41, 43, 50 and 51 were rejected under 35 U.S.C. 102(b) as anticipated by Nissim et al. as evidenced by Merchant et al. The Applicants traverse this rejection.

Under 35 U.S.C. §102, "A claim is anticipated only if each and every element as set forth in the claim is found either expressly or inherently described in a single prior art references." Verdegaal Bros. v. Union Oil of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The fact that a *certain* result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. MPEP § 2112. The prior art characteristic must be established as a certainty, probabilities are not sufficient. In re Oelrich, 666 F.2d 578, 581 (CCPA 1981).

Applicants claim 30 is directed to a method of preparing a multispecific antibody comprising a first polypeptide and at least one additional polypeptide, wherein(a)the first polypeptide comprises a first multimerization domain forming an interface positioned to interact with an interface of an additional multimerization domain of the at least one additional polypeptide,(b)the first and additional polypeptides each comprise a binding domain, the binding domain comprising a heavy chain variable domain and the same light chain variable domain, wherein each binding domain binds to a different antigen, and the first and additional multimerization domains interact with one another to form the multispecific antibody, the method comprising the steps of:(i)culturing a host cell comprising a nucleic acid encoding the first polypeptide and a nucleic acid encoding at least one additional polypeptide, wherein the culturing is such that the nucleic acids are expressed; and (ii)recovering the multispecific antibody from the host cell culture.

Applicants claim 43 is directed to a method of preparing a multispecific antibody comprising:(a)selecting a first nucleic acid encoding a first polypeptide comprising a heavy chain variable domain from an antibody specific for a first antigen, and a first

multimerization domain forming an interface that comprises an altered amino acid residue in the interface, and selecting at least one additional nucleic acid encoding at least one additional polypeptide comprising a heavy chain variable domain from an antibody specific for a second antigen and a second multimerization domain forming an interface, wherein the interface of the at least one additional polypeptide has an amino acid residue that specifically interacts with the altered amino acid residue in the interface on the first multimerization domain , thereby generating a stable interaction between the first and said additional polypeptides;(b)selecting a light chain encoding nucleic acid sequence, wherein the light chain variable domain associates with a binding region of each first and additional polypeptide of the multispecific antibody, wherein the binding region comprises a heavy chain variable domain and the light chain variable domain and wherein each binding region binds to a different antigen;(c)introducing into a host cell the first and additional nucleic acids and the light chain-encoding nucleic acid, and culturing the cell so that expression of the first and additional nucleic acids and the light chain-encoding nucleic acid occurs to form a multispecific antibody;(d) recovering the multispecific antibody from the cell culture.

Applicants claim 50 is directed to a method of preparing a multispecific antibody comprising a first polypeptide and at least one additional polypeptide, wherein (a) the first polypeptide comprises a multimerization domain forming an interface positioned to interact with an interface of a multimerization domain of the additional polypeptide,(b)the first and additional polypeptides each comprise a binding domain, the binding domain comprising a heavy chain and a common light chain, wherein the common light chain of the first and additional polypeptides has at least 98% sequence identity to a variable domain of a light chain of a first antibody and/or at least one additional antibody and only differs from each of the light chains of the first and/or at least one additional antibody at amino acid positions outside of the CDR regions, and wherein the first and at least one additional antibody bind to different antigens, and wherein each binding domain of the multispecific antibody binds to the different antigens, the method comprising the steps of:(i)culturing a host cell comprising nucleic acid encoding the first polypeptide and additional polypeptides, and the common light

chain, wherein the culturing is such that the nucleic acid is expressed; and(ii)recovering the multispecific antibody from the host cell culture.

Applicants submit Nissim et al. does not teach all of the elements of Applicants' claims. Applicants submit that Nissim et al. is directed to the development of a library of V_H scFv with randomized CDRH3 regions for isolating an antibody or fragment thereof that binds to a single antigen. The phage library is screened against single antigens separately and there is no teaching or suggestion in this reference that a multispecific antibody comprising at least two binding domains that bind to different antigens can or should be made using the process as described in Nissim et al. In contrast, the methods as claimed provide for production of a multispecific antibody that comprises at least two binding domains that bind to different antigens.

There is no teaching or suggestion in the Nissim reference that multispecific antibodies can or should be formed wherein each binding domain binds to a different antigen and has the same light chain. The Nissim et al. reference does not teach or even suggest Applicants highly efficient method of making heteromultimeric multispecific antibodies by, not only incorporating common light chains, but also by incorporating multimerization domains that interact with one another, which multimerization domains are useful for increasing specific heterodimeric association of the polypeptides, thereby producing multispecific antibodies. As provided in Applicants' originally filed specification, the multimerization domain promotes interaction between a specific first polypeptide and a specific second polypeptide, thereby enhancing the formation of the desired heteromultimer and substantially reducing the probability of the formation of undesired heteromultimers or homomultimers (see page 19, line 15 to page 21, line 2, and particularly page 19, lines 19-24 of the specification).

With respect to the examiner's comments regarding " multimers" in Nissim et al., Applicants submit these comments miss the significance of Applicant's invention and it's difference from anything that is disclosed in Nissim et al. The "multimers" in Nissim et al. were actually aggregates formed randomly by such conditions as concentration during purification, or acid elution and neutralization during purification of single chain Fv polypeptides that have single antigen specificity (see Nissim et al., page 695, column 2, second full paragraph to page 696, column 1). In addition, on page 696, col. 1, Nissim et

al. disclose that it is desirable to drive the self-aggregation of scFv fragments. Such self-aggregation teaches monospecificity of an aggregate and random association of the monomers and thus, teaches away from Applicants' invention of a method of preparing multichain, multispecific antibodies wherein the different polypeptides of the multispecific antibody associate with one another by specific interactions of the multimerization domains, and wherein the polypeptides form different antigen binding domains with the same light chain. There is no showing in Nissim et al. those multimerization domains which interact with one another to form heteromultimeric multispecific antibodies as claimed by Applicants are formed in the random, self-aggregates of Nissim et al. Thus, Nissim et al. does not teach or suggest Applicants' claimed invention.

Applicants submit that, at least for these reasons, the Nissim et al. reference does not disclose all of the elements of Applicants' claims and, therefore, does not anticipate the claims. Applicants request withdrawal of the rejection.

Interview

The Applicants thank the Examiner for acknowledging Applicants' request for an interview, and inviting Applicants to request an interview prior to filing a Response to the present Office Action.

Summary

Applicants submit that the claims are in condition for allowance and notification to that effect is earnestly solicited. The Examiner is invited to contact Applicants' representative if prosecution may be assisted thereby.

Respectfully submitted,

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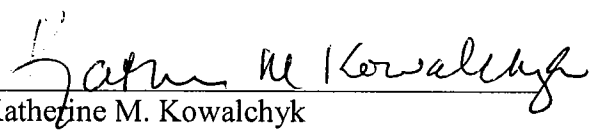

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